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(54) Title: SUBSTITUTED QUINOXALINE DERIVATIVES AS INTERLEUKIN-8 RECEPTOR ANTAGONISTS

(57) Abstract

Quinoxaline compounds are described as well as method for the preparation and pharmaceutical compositions of same, which are useful as interleukin-8 (IL-8) receptor antagonists and can be used in the treatment of a chemokine-mediated disease wherein the chemokine binds to an IL-8a (CXCR1) or b (CXCR2) receptor such as, a chemokine-mediated disease selected from psoriasis, or atopic dermatitis, disease associated with pathological angiogenesis (i.e. cancer), asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulo-nephritis, or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections.

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SUBSTITUTED QUINOXALINE DERIVATIVES AS INTERLEUKIN-8 RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

The present invention relates to novel quinoxaline compounds useful as pharmaceutical agents, to methods for their production, to pharmaceutical compositions which include these compounds and a pharmaceutical carrier, and to pharmaceutical methods of treatment. The compounds of the present invention are Interleukin-8 (IL-8) receptor antagonists. More particularly, the compounds of the present invention are useful in the treatment of a chemokine-mediated disease wherein the chemokine binds to an IL-8a (CXCR1) or b (CXCR2) receptor such as, for example, a chemokine-mediated disease selected from psoriasis, or atopic dermatitis, tumor growth and angiogenesis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulo-nephritis, or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections.

IL-8 is a 72 amino acid protein which is a member of the superfamily of leukocyte chemoattractant proteins which have been referred to as intercrines, C-X-C or C-C cytokines or, more recently as chemokines (Oppenheim J.J. et al., "Properties of the novel proinflammatory supergene "intercrine" cytokine family." *Annu. Rev. Immunol.*, 1991;9:617-648). Many members of the chemokine family appear to be involved in the inflammatory process and in the trafficking of leukocytes. The chemokine superfamily is composed of two branches: the α- and the β-chemokines. The α-chemokine branch includes IL-8, neutrophil activating peptide-2 (NAP-2), melanoma growth stimulatory activity (MGSA/gro or GROα), and ENA-78, all of which have attracting and activating effects predominantly on neutrophils. This branch also includes PF4, β-thromboglobulin, and CTAPIII, which do not affect neutrophils.

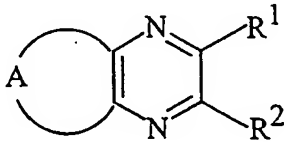
IL-8 was originally identified by its ability to both attract and activate polymorphonuclear leukocytes (neutrophils) and has now been shown to be rapidly induced in a wide variety of cell and tissue types in response to pro-inflammatory cytokines such as IL-1b or TNFα. Additionally, there is data demonstrating high systemic levels of IL-8 in certain neutrophil-mediated inflammatory diseases, suggesting the IL-8 and closely related factors may be the principal endogenous mediators of neutrophil activation. Many reports have been published regarding disorders in which high levels of IL-8 have been measured, and include rheumatoid arthritis, septic shock, asthma, cystic fibrosis, myocardial infarction, and psoriasis (Baggiolini et al., *FEBS Lett.*, 1992;307:97; Miller et al., *Crit. Rev. Immunol.*, 1992;12:17. Oppenhein et al., *Annu. Rev. Immunol.*, 1991;9:617; Seitz et al., *J. Clin. Invest.*, 1991;87:463; Miller et al., *Am. Rev. Respir. Dis.*, 1992;146:427; Donnely et al., *Lancet*, 1993;341:643). Strong in vivo evidence indicating a central role of IL-8 in the pathology related to lung ischemia/reperfusion has recently been published (Sekido N., Mukaida N. et al., "Prevention of lung reperfusion injury in rabbits by a monoclonal antibody against interleukin-8." *Nature*, 1993;365(6447):654-7 Issn: 0028-0836). A monoclonal antibody to rabbit IL-8, capable of blocking the in vitro neutrophil chemotactic activity of IL-8, prevented tissue damage in the rabbit lung normally resulting from lung ischemia/reperfusion. More recently, another study has shown beneficial effects of an IL-8 neutralizing antibody in an endotoxin-induced pleurisy model in rabbit (Broaddus V.C., Boylan A.M. et al., "Neutralization of IL-8 inhibits neutrophil influx in a rabbit model of endotoxin-induced pleurisy," *J. Immunol.*, 1994;152(6):2960-2967). There were also reports indicating similar beneficial effects with IL-8 neutralizing antibodies in animal models of dermatitis, joint arthritis, and glomerulonephritis. Additionally, knockout mice have been generated in which the apparent mouse homologue of the IL-8R (closer to IL-8RB) was deleted by homologous recombination (Cacalano G., Lee J. et al., "Neutrophil and b cell expansion in mice that lack the murine IL-8 receptor homolog," *Science*, 1994;265(5172):682-4 Issn: 0036-8075). Although these mice appear healthy, their neutrophils are greatly impaired, as compared to wild-type mice, in their ability to migrate to the peritoneum in response to intraperitoneal

thioglycollate injection. All of these results suggest that IL-8 is an important mediator of neutrophil migration and activity in some inflammatory settings, and that a small molecule antagonist to the receptors for IL-8 should prove to be an effective treatment for some inflammatory pathologies and has the potential to be a broadly useful anti-inflammatory agent. Also, there have been reports that IL-8 is an important cytokine involved in tumor growth and angiogenesis in a variety of malignancies (Hebert et al., *Cancer Invest.*, 1993;11:743 and Richards et al., *American Journal of Surgery,* 1997;174:507).

We have identified a series of quinoxalines that are IL-8 receptor antagonists and which can additionally be used in psoriasis, or atopic dermatitis, disease associated with pathological angiogenesis (i.e. cancer), asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulo-nephritis, or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections.

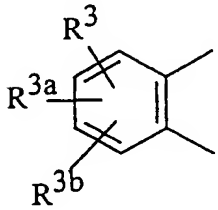
SUMMARY OF THE INVENTION

Accordingly, a first aspect of the present invention is a compound of Formula I



I

wherein A is selected from the group consisting of:



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein

R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

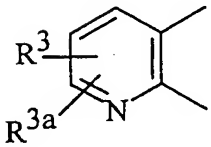
halogen,

CF_3,

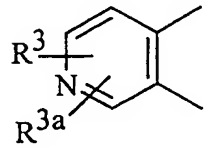
CBr_3,

CCl_3, or

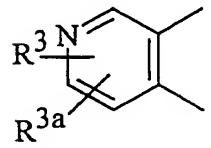
NO_2,



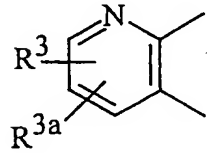
wherein R^3 and R^{3a} are as defined above,



wherein R^3 and R^{3a} are as defined above,



wherein R^3 and R^{3a} are as defined above,



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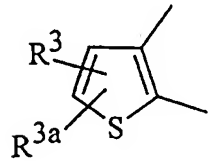

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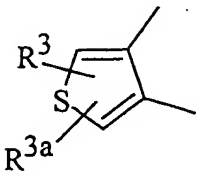
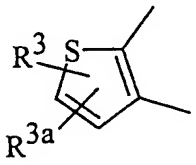
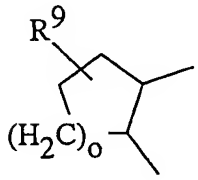
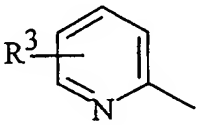
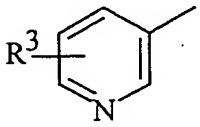

wherein R^3 and R^{3a} are as defined above,


wherein R^3 and R^{3a} are as defined above,


wherein o is an integer of 1 or 2, and R^9 is hydrogen or alkyl;

R^1 is 
wherein R^3 is as defined above,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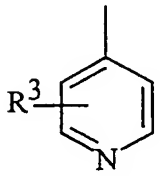
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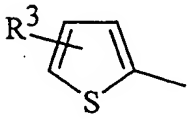
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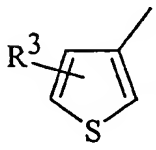
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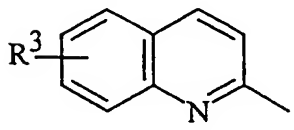
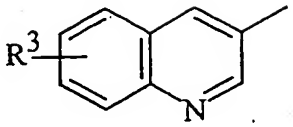
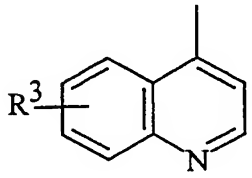
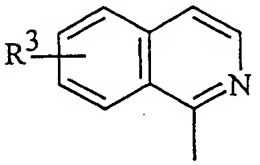
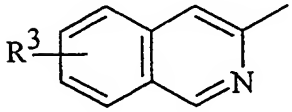
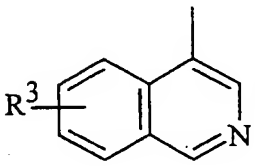

wherein R^3 is as defined above,

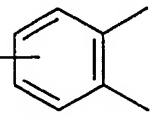
 wherein R^3 is as defined above,

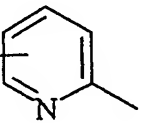
 wherein R^3 is as defined above,

 wherein R^3 is as defined above,

 wherein R^3 is as defined above, or

 wherein R^3 is as defined above, with the proviso that

when A is  wherein R^3 is hydrogen, methyl, or chloro,

R^1 is not  wherein R^3 is hydrogen; and

R^2 is CF_3,

CCl_3,

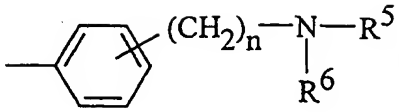
CBr_3, or

$-N-R^{10}$ wherein R^{10} is
R^{11}

hydrogen,

alkyl,

aralkyl, or

 wherein n, R^5, and R^6 are

as defined above, and

R^{11} is $-(CH_2)_m-N(R^6)-R^5$ wherein R^5, R^6, and m are as defined above,

$-(CH_2)_m-N(R^{12})-C(=N-R^{13})-N-R^{12a}$ wherein R^{12} and R^{12a} are each

independently the same or different and are hydrogen, alkyl,

or aryl, and

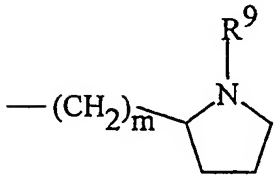
R^{13} is hydrogen or alkyl, and

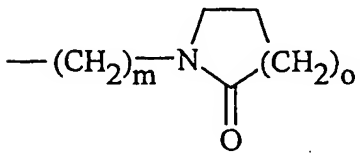
m is as defined above,

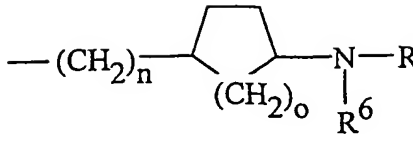
$-(CH_2)_m-C(=N-R^{13})-N(R^{12a})-R^{12}$ wherein m, R^{12}, R^{12a},

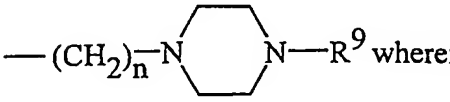
and R^{13} are as defined above,

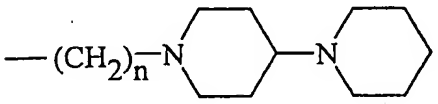
wherein R^9 and m are as defined above,

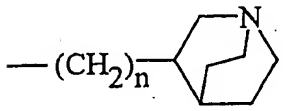
 wherein R^9 and m are as defined above,

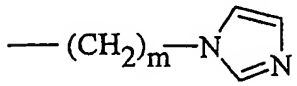
 wherein m and o are as defined above,

 wherein n, o, R^5, and R^6 are as defined above,

 wherein n and R^9 are as defined above,

 wherein n is as defined above,

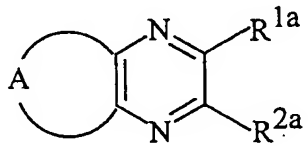
 wherein n is as defined above,

 wherein m is as defined above, or

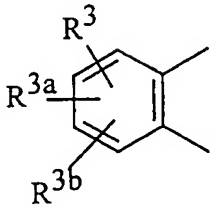
R^{10} and R^{11} when taken together can form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 is as defined above;

or a pharmaceutically acceptable salt thereof.

A second aspect of the present invention is a method of treating a chemokine-mediated disease state, wherein the chemokine binds to an IL-8a (CXCR1) or b (CXCR2) receptor in a mammal, which comprises administering to said mammal an effective amount of compound of Formula II

 II

wherein A is selected from the group consisting of:



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or

R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

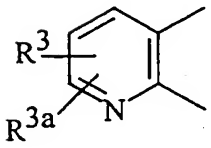
halogen,

CF_3,

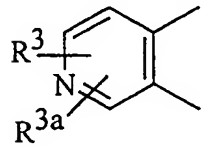
CBr_3,

CCl_3, or

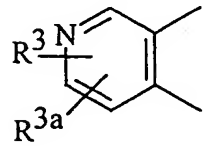
NO_2,



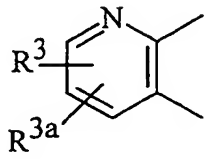
wherein R^3 and R^{3a} are as defined above,

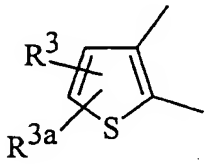


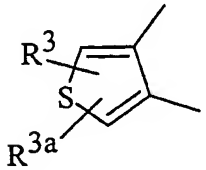
wherein R^3 and R^{3a} are as defined above,

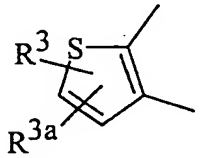


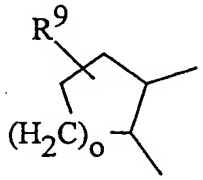
wherein R^3 and R^{3a} are as defined above,

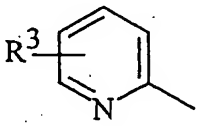

wherein R^3 and R^{3a} are as defined above,

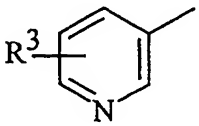

wherein R^3 and R^{3a} are as defined above,

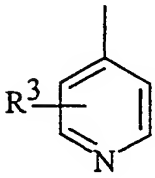

wherein R^3 and R^{3a} are as defined above,

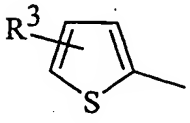

wherein R^3 and R^{3a} are as defined above,

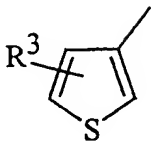

wherein o is an integer of 1 or 2, and R^9 is hydrogen or alkyl;

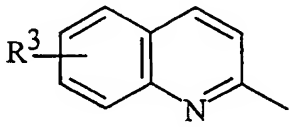
R^{1a} is 
wherein R^3 is as defined above,

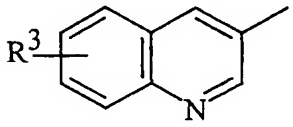

wherein R^3 is as defined above,

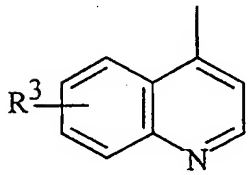

wherein R^3 is as defined above,

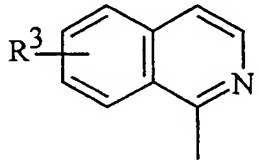

wherein R^3 is as defined above,

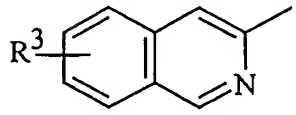
 wherein R^3 is as defined above,

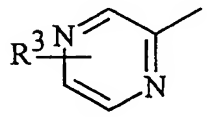
 wherein R^3 is as defined above,

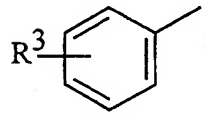
 wherein R^3 is as defined above,

 wherein R^3 is as defined above,

 wherein R^3 is as defined above,

 wherein R^3 is as defined above,

 wherein R^3 is as defined above,

 wherein R^3 is as defined above,

alkyl,

OR^4 wherein R^4 is as defined above, or

$-(CH_2)_n-N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above; and

R^{2a} is CF_3,

CCl_3,

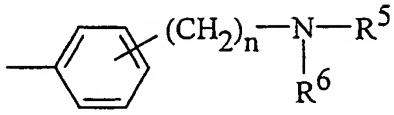
CBr_3, or

$-N-R^{10}$ wherein R^{10} is
|
R^{11}

hydrogen,

alkyl,

aralkyl, or



wherein n, R^5, and R^6 are as defined above, and

R^{11} is $-(CH_2)_m-N-R^5$ wherein R^5, R^6, and m are as defined
|
R^6

above,

$-(CH_2)_m-\underset{\|}{\overset{N-R^{13}}{C}}-N-R^{12}$ wherein R^{12} and R^{12a} are each
| |
R^{12} R^{12a}

independently the same or different and are

hydrogen,

alkyl, or

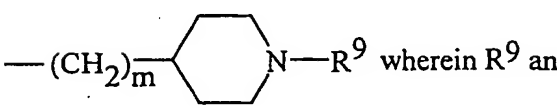
aryl, and

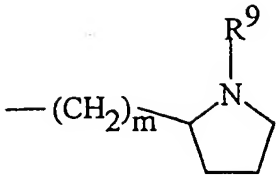
R^{13} is hydrogen or alkyl, and

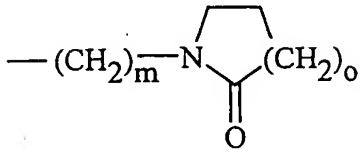
m is as defined above,

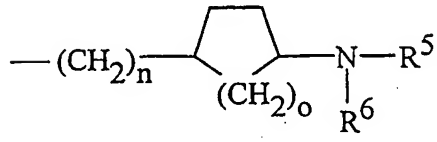
$-(CH_2)_m-\underset{\|}{\overset{N-R^{13}}{C}}-N-R^{12}$ wherein m, R^{12}, R^{12a}, and R^{13} are as
|
R^{12a}

defined above,

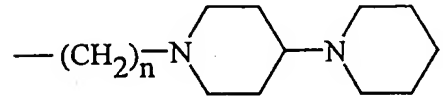
 wherein R^9 and m are as defined above,

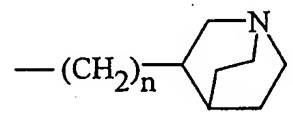

wherein R^9 and m are as defined above,

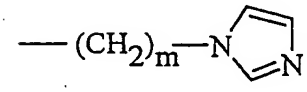

wherein m and o are as defined above,


wherein n, o, R^5, and R^6 are as defined above,

wherein n and R^9 are as defined above,


wherein n is as defined above,


wherein n is as defined above,


wherein m is as defined above, or

R^{10} and R^{11} when taken together can form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 is as defined above;

or a pharmaceutically acceptable salt thereof.

As inhibitors of chemokine-mediated diseases, the compounds of Formula I and II can be used as agent for treating psoriasis, or atopic dermatitis, disease associated with pathological angiogenesis (i.e. cancer), asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome,

stroke, cardiac and renal reperfusion injury, glomerulo-nephritis, or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections.

A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of a compound of Formula I or Formula II in unit dosage form in the treatment methods mentioned above. Finally, the present invention is directed to methods for production of compounds of Formula I or Formula II.

DETAILED DESCRIPTION OF THE INVENTION

In the compounds of Formula I or II, the term "alkyl" means a straight or branched hydrocarbon radical having from 1 to 8 carbon atoms and includes, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, sec-butyl, isobutyl, tert-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, and the like.

"Alkoxy" and "thioalkoxy" are O-alkyl or S-alkyl of from 1 to 6 carbon atoms as defined above for "alkyl".

The term "aryl" means an aromatic radical which is a phenyl group, a phenyl group substituted by 1 to 4 substituents selected from alkyl as defined above, alkoxy as defined above, thioalkoxy as defined above, hydroxy, halogen, trifluoromethyl, amino, alkylamino as defined above for alkyl, dialkylamino as defined for alkyl, nitro, cyano, carboxy, SO_3H, CHO, $-\overset{O}{\overset{\|}{C}}$-alkyl as defined above for alkyl, $-\overset{O}{\overset{\|}{C}}-NH_2$, $-\overset{O}{\overset{\|}{C}}-NH$-alkyl as defined above for alkyl, $-\overset{O}{\overset{\|}{C}}-N(alkyl)_2$ as defined above for alkyl, $-(CH_2)_n-NH_2$ wherein n is an integer of 1 to 5, $-(CH_2)_n$-NH-alkyl as defined above for alkyl and n, $-(CH_2)_n-N(alkyl)_2$ as defined above for alkyl and n.

The term "aralkyl" or "arylalkyl" means an aromatic radical attached to an alkyl radical wherein "aryl" and "alkyl" are as defined above, for example, benzyl, fluorenylmethyl, and the like.

The term "5- to 7-membered ring optionally containing an oxygen atom or N-R^4" includes, for example, pyrrolidine, pyrrazolidine, imidazolidine, oxazolidine, piperidine, piperazine, morpholine, homopiperidine, and the like. The carbon atoms of the above 5- to 7-membered ring may be substituted independently by alkyl, amino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxy, carboxyalkyl, alkylcarboxyalkyl, thio, thioalkyl, alkylthioalkyl, hydroxy, hydroxyalkyl, alkoxy, or alkoxyalkyl.

"Halogen" is fluorine, chlorine, bromine, or iodine.

Some of the compounds of Formula I or II are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I or II include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M. et al, "Pharmaceutical Salts," *J. of Pharma Sci.*, 1977;66:1).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain

physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

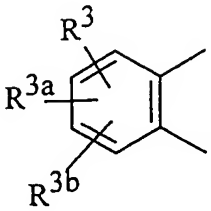
Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N′-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *J. of Pharma Sci.*, 1977;66:1).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

A preferred compound of Formula I in the first aspect of the present invention is one wherein A is selected from the group consisting of:



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined

above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 and m are as defined above,

$-(CH_2)_n-CON-R^7$ wherein R^7, R^8, and n are as defined above,

R^8

$-(CH_2)_n-SO_2N-R^7$ wherein R^7, R^8, and n are as defined above,

R^8

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

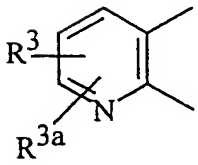
halogen,

CF_3,

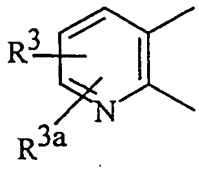
CBr_3,

CCl_3, or

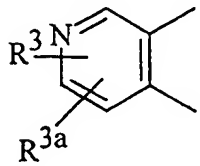
NO_2,



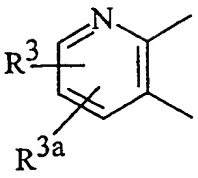
wherein R^3 and R^{3a} are as defined above,



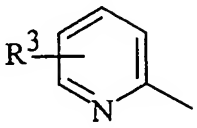
wherein R^3 and R^{3a} are as defined above,

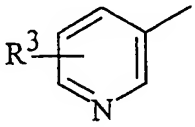


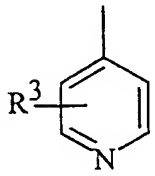
wherein R^3 and R^{3a} are as defined above, or



wherein R^3 and R^{3a} are as defined above;

R^1 is  wherein R^3 is as defined above,

 wherein R^3 is as defined above,

 wherein R^3 is as defined above; and

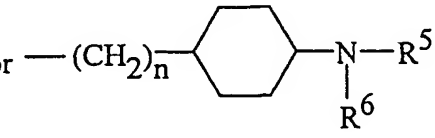
R^2 is CF_3,

CCl_3,

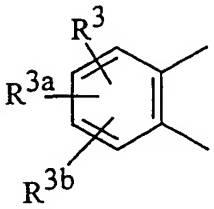
CBr_3, or

$-N(R^{10})-R^{11}$ wherein R^{10} is hydrogen and

R^{11} is $-(CH_2)_n-N(R^6)-R^5$ wherein n, R^5, and R^6 are as defined above,

or  wherein n, R^5, and R^6 are as defined above.

A more preferred compound of Formula I in the first aspect of the present invention is one wherein A is



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined

above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

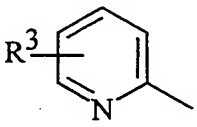
halogen,

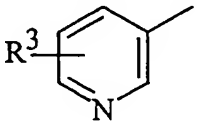
CF_3,

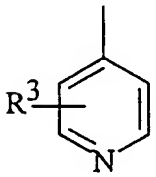
CBr_3,

CCl_3, or

NO_2;

R^1 is  wherein R^3 is as defined above,

 wherein R^3 is as defined above, or

 wherein R^3 is as defined above; and

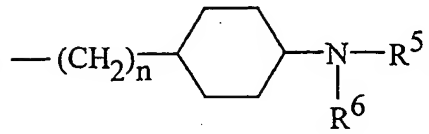
R^2 is CF_3,

CCl_3,

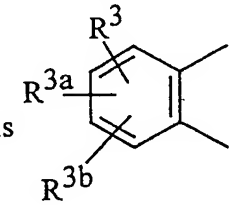
CBr_3, or

$-N-R^{10}$ wherein R^{10} is hydrogen and
|
R^{11}

R^{11} is $-(CH_2)_n-N-R^5$ wherein n, R^5, and R^6 are as defined above,
|
R^6

or  wherein n, R^5, and R^6 are as defined above.

Another more preferred compound of Formula I in the first aspect of the present invention is one wherein

A is  wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N-R^5$ wherein R^5 and R^6 are each the same or
|
R^6

different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

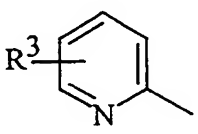
halogen,

CF_3,

CBr_3,

CCl_3, or

NO_2;

R^1 is  wherein R^3 is as defined above; and

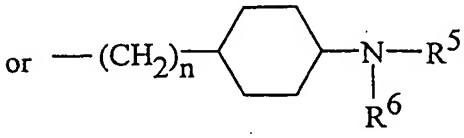
R^2 is CF_3,

CCl_3,

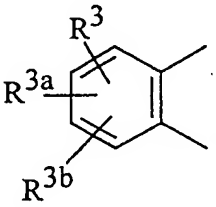
CBr_3, or

-N-R^{10} wherein R^{10} is hydrogen and
|
R^{11}

R^{11} is -$(CH_2)_n$-N-R^5 wherein n, R^5, and R^6 are as defined above,
|
R^6

or  wherein n, R^5, and R^6 are as defined above.

A most preferred compound of Formula I in the first aspect of the present invention is one wherein

A is  wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

-OR^4 wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

-$(CH_2)_m$-N-R^5 wherein
|
R^6

R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 an m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

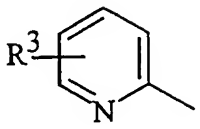
halogen,

CF_3,

CBr_3,

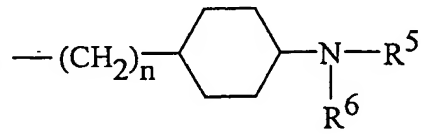
CCl_3, or

NO_2;

R^1 is  wherein R^3 is as defined above; and

R^2 is -N-R^{10} wherein R^{10} is hydrogen and
|
R^{11}

R^{11} is -$(CH_2)_n$-N-R^5 wherein n, R^5, and R^6 are as defined above,
|
R^6

or  wherein n, R^5, R^6 are as defined above.

Particularly valuable in the first aspect of the present invention is a compound selected from the group consisting of:

N-(1-azabicyclo[2.2.2]octan-3-yl)-3-(2-pyridinyl)-2-quinoxalinamine;

N-[3-(1H-imidazol-1-yl)propyl]-3-(2-pyridinyl)-2-quinoxalinamine;

N-[2-(1-methyl-2-pyrrolidinyl)ethyl]-3-(2-pyridinyl)-2-quinoxalinamine;

1-[3-[[3-pyridinyl)-2-quinoxalinamine]amino]propyl]-2-pyrrolidinone;

N-[4-(4-morpholinyl)phenyl]-3-(2-pyridinyl)-2-quinoxalinamine;

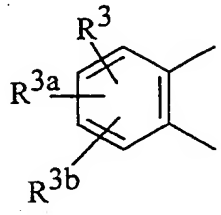
N-(4-piperidinylmethyl)-3-(2-pyridinyl)-2-quinoxalinamine;

N-[4-(dimethylamino)phenyl]-3-(2-pyridinyl)-2-quinoxalinamine; and

N-methyl-N-[4-[[3-(2-pyridinyl)-2-quinoxalinyl]amino]phenyl]-acetamide;

or a pharmaceutically acceptable salt thereof.

A preferred compound of Formula II in the second aspect of the present invention is one wherein A is selected from the group consisting of:



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein

R^5 and R^6 are each the same or different and are hydrogen, alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined

above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 and m are as defined above,

$-(CH_2)_n-CON-R^7$ wherein R^7, R^8, and n are as defined above,

$$\begin{array}{l} \\ | \\ R^8 \end{array}$$

$-(CH_2)_n-SO_2N-R^7$ wherein R^7, R^8, and n are as defined above,

$$\begin{array}{l} \\ | \\ R^8 \end{array}$$

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

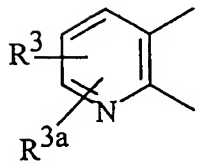
halogen,

CF_3,

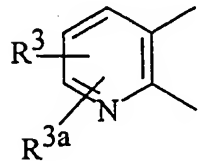
CBr_3,

CCl_3, or

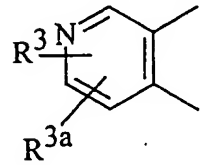
NO_2,



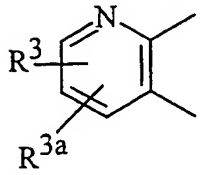
wherein R^3 and R^{3a} are as defined above,



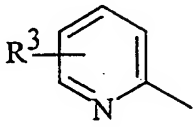
wherein R^3 and R^{3a} are as defined above,

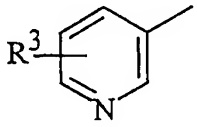


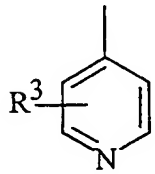
wherein R^3 and R^{3a} are as defined above, or



wherein R^3 and R^{3a} are as defined above;

R^{1a} is  wherein R^3 is as defined above,

 wherein R^3 is as defined above, or

 wherein R^3 is as defined above; and

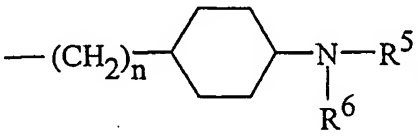
R^{2a} is CF_3,

CCl_3,

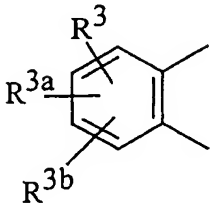
CBr_3, or

$-N(R^{10})-$ wherein R^{10} is hydrogen and
$|$
R^{11}

R^{11} is $-(CH_2)_n-N(R^6)-R^5$ wherein n, R^5, and R^6 are as defined above,

or  wherein n, R^5, and R^6 are as defined above.

A more preferred compound of Formula II in the second aspect of the present invention is one wherein A is



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein

R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined

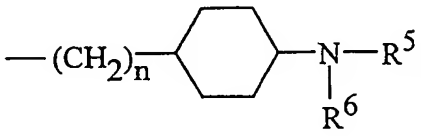
above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 and m are as defined above,

$-(CH_2)_n-CON-R^7$ wherein R^7, R^8, and n are as defined above,
$\quad\quad\quad

$-N(R^{11})-R^{10}$ wherein R^{10} is hydrogen and

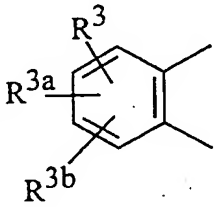
R^{11}

R^{11} is $-(CH_2)_n-N(R^6)-R^5$ wherein n, R^5, R^6 are as defined above, or



wherein n, R^5, R^6 are as defined above.

Another more preferred compound of Formula II in the second aspect of the present invention is one wherein

A is  wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein

R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and

m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or

R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 and m are is as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

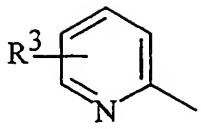
halogen;

CF_3,

CBr_3,

CCl_3, or

NO_2;

R^{1a} is  wherein R^3 is as defined above; and

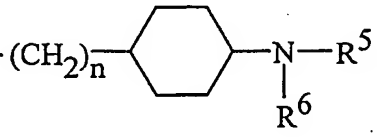
R^{2a} is CF_3,

CCl_3,

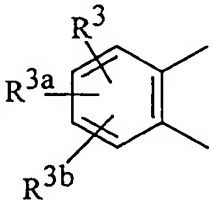
CBr_3, or

$-N(R^{10})(R^{11})$ wherein R^{10} is hydrogen and

R^{11} is $-(CH_2)_n-N(R^6)-R^5$ wherein n, R^5, and R^6 are as defined above,

or  wherein n, R^5, and R^6 are as defined above.

A most preferred compound of Formula II in the second aspect of the present invention is one wherein

A is  wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein

R^5 and R^6 are each the same or different and are hydrogen, alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

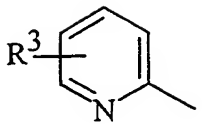
halogen,

CF_3,

CBr_3,

CCl_3, or

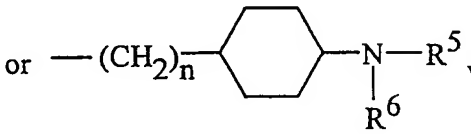
NO_2;

R^{1a} is  wherein R^3 is as defined above; and

R^{2a} is

$-N-R^{10}$ wherein R^{10} is hydrogen and
$|$
R^{11}

R^{11} is $-(CH_2)_n-N-R^5$ wherein n, R^5, and R^6 are as defined above,
$|$
R^6

or  wherein n, R^5, R^6 are as defined above.

Particularly valuable in the second aspect of the present invention is a compound selected from the group consisting of:

N′-[6-Chloro-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-diethyl-1,2-ethanediamine;

N′-[7-Chloro-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-diethyl-1,2-ethanediamine;

N′-[6,7-Dichloro-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-diethyl-1,2-ethanediamine;

6,7-Dichloro-3-(2-pyridinyl)-N-[3-(1-pyrrolidinyl)propyl]-2-quinoxalinamine;

6-Chloro-3-(2-pyridinyl)-N-[2-(1-pyrrolidinyl)ethyl]-2-quinoxalinamine;

7-Chloro-3-(2-pyridinyl)-N-[2-(1-pyrrolidinyl)ethyl]-2-quinoxalinamine;

N′-[6,7-Dimethyl-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-diethyl-1,2-ethanediamine;

6-Chloro-3-(2-pyridinyl)-N-[3-(1-pyrrolidinyl)propyl]-2-quinoxalinamine;

7-Chloro-3-(2-pyridinyl)-N-[3-(1-pyrrolidinyl)propyl]-2-quinoxalinamine;

N′-[6,7-Dimethyl-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-dimethyl-1,3-propanediamine;

N′-[6-Chloro-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-dimethyl-1,3-propanediamine;

N′-[7-Chloro-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-dimethyl-1,3-propanediamine;

6-Chloro-N-[4-(dimethylamino)cyclohexyl]-3-(2-pyridinyl)-2-quinoxalinamine;

7-Chloro-N-[4-(dimethylamino)cyclohexyl]-3-(2-pyridinyl)-2-quinoxalinamine;

2,6,7-Trimethyl-3-piperazin-1-yl-quinoxaline;

N,N-Dimethyl-N′-(3-methyl-quinoxalin-2-yl)-propane-1,3-diamine;

2-Methyl-3-(4-methyl-piperazin-1-yl)-quinoxaline;

2-Ethyl-3-piperazin-1-yl-quinoxaline;

6,7-Dichloro-2-methyl-3-piperazin-1-yl-quinoxaline;

2-Phenyl-3-piperidin-1-yl-quinoxaline;

Benzyl-(3-phenyl-quinoxalin-2-yl)-amine;

Phenyl-(3-phenyl-quinoxalin-2-yl)-amine;

Methyl-(3-phenyl-quinoxalin-2-yl)-amine;

3-Phenyl-quinoxalin-2-ylamine;

2-Methyl-3-piperazin-1-yl-quinoxaline;

2-Methyl-3-piperidino-quinoxaline;

5-[4-(3-Methyl-quinoxalin-2-yl)-piperazin-1-yl]-pentan-1-ol;

N,N-Dimethyl-N′-(3-methyl-quinoxalin-2-yl)-ethane-1,2-diamine;

N,N-Diethyl-N′-(3-methyl-quinoxalin-2-yl)-ethane-1,2-diamine;

(3-Methyl-quinoxalin-2-yl)-(3-morpholin-4-yl-propyl)-amine;

N,N-Dimethyl-N′-(3-phenyl-quinoxalin-2-yl)-propane-1,3-diamine;

3-Phenyl-quinoxalin-2-ylamine;

2-Methyl-3-pyrrolidin-1-yl-quinoxaline;

N-(1-Azabicyclo[2.2.2]octan-3-yl)-3-(2-pyridinyl)-2-quinoxalinamine;

N-[3-(1H-Imidazol-1-yl)propyl]-3-(2-pyridinyl)-2-quinoxalinamine;

N-[2-(1-Methyl-2-pyrrolidinyl)ethyl]-3-(2-pyridinyl)-2-quinoxalinamine;
1-[3-[[3-Pyridinyl)-2-quinoxalinamine]amino]propyl]-2-pyrrolidinone;
N-[4-(4-Morpholinyl)phenyl]-3-(2-pyridinyl)-2-quinoxalinamine;
N-(4-Piperidinylmethyl)-3-(2-pyridinyl)-2-quinoxalinamine;
N-[4-(Dimethylamino)phenyl]-3-(2-pyridinyl)-2-quinoxalinamine; and
N-Methyl-N-[4-[[3-(2-pyridinyl)-2-quinoxalinyl]amino]phenyl]-acetamide; or a pharmaceutically acceptable salt thereof.

The compounds of Formula I and II are valuable receptor antagonists of IL-8.

The IL-8 chemokine inhibitory effects of compounds of the present invention were determined by the following procedures:

Chemotaxis Assay

Compounds of Formula I and II were evaluated for their effect on chemotaxis using methodology known in the art, e.g., Carr M.W., Roth S.J., Luther E., Rose S.S., and Springer T.A., "Monocyte chemoattractant protein 1 acts as a T-lymphocyte chemoattractant." *Proc. Natl. Acad. Sci. USA*, 1994;91:3652; Qin S., Larosa G., Campbell J.J. et al., "Expression of MCP-1 and IL-8 receptors on subset on T-cells, and correlation with transendothelial chemotactic potential," *Eur. J. Immu.*, 1996;26:640.

Briefly, freshly isolated human neutrophils were resuspended in chemotaxis buffer, which is made of one part of RPMI 1640 medium, one part of Medium 199, and 0.5% BSA. The cells were incubated with or without compounds for 5 minutes. Similarly, rhIL-8 was incubated in a separate plate, then transferred into lower chambers of chemotaxis plate. Neutrophils were added onto the top chamber. The plates were incubated at 37°C for 30 minutes. The top chamber was then removed and the plate frozen at -80°C for 30 minutes. After thawing, migrated cells were stained with Cytoquant Cell Proliferation Assay Kit (Molecular Probes No. C-7026) and quantitated by reading the plate on a fluorescent plate reader.

Calcium Flux Assay

Compounds of Formula I and II were evaluated for their effect on calcium flux using methodology known in the art, e.g., Neote K., DiGregorio D., Mak J.Y., Horuk R., and Schall T.J., "Molecular cloning, functional expression, and signaling characteristics of a C-C chemokine receptor," *Cell*, 1993;72:415.

Briefly, human neutrophils were incubated with the fluorescence dye FLUO-3 for 1 hour. The cells were washed after this loading period, resuspended in HANKs buffer, and loaded into a 96-well plate. Compound was added to each well. After a 2-minute incubation period, the cells were stimulated with human IL-8 and the calcium flux response recorded and quantified.

The data in Table 1 shows the effect of a representative compound of the present invention on chemotaxis and calcium flux.

TABLE 1

Example	IL-8 Chemotaxis (IC_{50} = μM)	IL-8 Ca^{+2} Flux % Inhibition (μM)
1	0.89	34% @ 11

The compounds of Formula I and II may be obtained by applying synthetic methodology known in the art, such as, for example, Werbel L. et al., *J. Med. Chem.*, 1968;11:630; Moderhack D., et al., *Chem. Ber.*, 1994:1633; Loriga M, et al., *Farmaco*, 1995;50(5):289; *Chin. Chem. Lett.*, 1990;1(3):25; Shepard T. and Smith D.M., *J. Chem. Soc.*, Perkin Trans I, 1987;3(501):11.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or II or a corresponding pharmaceutically acceptable salt of a compound of Formula I or II.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 1 mg to 1000 mg, preferably 10 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents for the treatment of psoriasis, or atopic dermatitis, disease associated with pathological angiogenesis (i.e. cancer), asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulo-nephritis, or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections, the compounds utilized in the pharmaceutical method of this invention can be administered at the initial dosage of about 1 mg to about 100 mg per kilogram

daily. A daily dose range of about 25 mg to about 75 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

6-Chloro-N-[4-(dimethylamino)cyclohexyl]-3-(2-pyridinyl)-2-quinoxalinamine and 7-Chloro-N-[4-(dimethylamino)cyclohexyl]-3-(2-pyridinyl)-2-quinoxalinamine, dihydrochloride, hydrate; mp 151-153°C.

EXAMPLE 2

N-(1-Azabicyclo[2.2.2]octan-3-yl)-3-(2-pyridinyl)-2-quinoxalinamine; mp 63-65°C.

EXAMPLE 3

N-[3-(1H-Imidazol-1-yl)propyl]-3-(2-pyridinyl)-2-quinoxalinamine; mp 85-86°C.

EXAMPLE 4

N-[2-(1-Methyl-2-pyrrolidinyl)ethyl]-3-(2-pyridinyl)-2-quinoxalinamine; mp 186-188°C.

EXAMPLE 5

1-[3-[[3-Pyridinyl)-2-quinoxalinamine]amino]propyl]-2-pyrrolidinone; pale amber viscous liquid.

EXAMPLE 6

N-[4-(4-Morpholinyl)phenyl]-3-(2-pyridinyl)-2-quinoxalinamine; mp 205-206°C.

EXAMPLE 7

N-(4-Pyridinylmethyl)-3-(2-pyridinyl)-2-quinoxalinamine; mp 142-144°C.

EXAMPLE 8

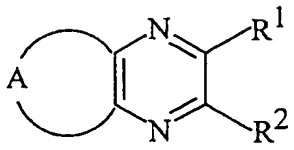
N-[4-(Dimethylamino)phenyl]-3-(2-pyridinyl)-2-quinoxalinamine; mp 169-170°C.

EXAMPLE 9

N-Methyl-N-[4-[[3-(2-pyridinyl)-2-quinoxalinyl]amino]phenyl]-acetamide; mp 165-166°C.

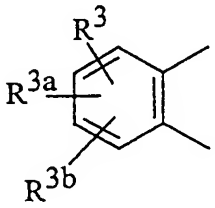
CLAIMS

1. A compound of Formula I



I

wherein A is selected from the group consisting of:



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein

R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8

are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 and m are as defined above,

$-(CH_2)_n-CON-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

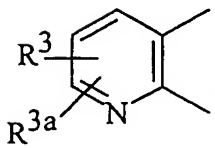
halogen,

CF_3,

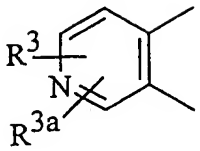
CBr_3,

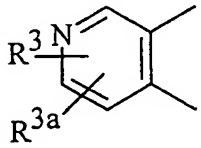
CCl_3, or

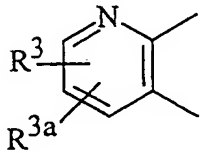
NO_2,

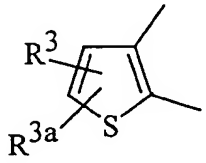


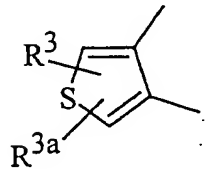
wherein R^3 and R^{3a} are as defined above,

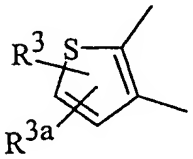

wherein R^3 and R^{3a} are as defined above,

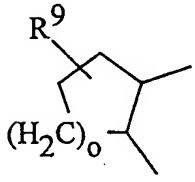

wherein R^3 and R^{3a} are as defined above,

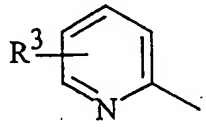

wherein R^3 and R^{3a} are as defined above,

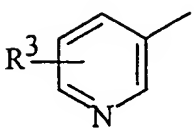

wherein R^3 and R^{3a} are as defined above,

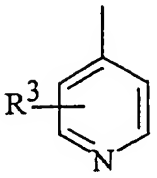

wherein R^3 and R^{3a} are as defined above,

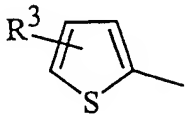

wherein R^3 and R^{3a} are as defined above,

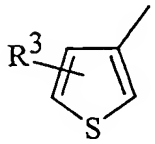

wherein o is an integer of 1 or 2, and R^9 is hydrogen or alkyl;

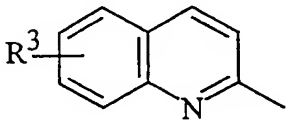
R^1 is 
wherein R^3 is as defined above,

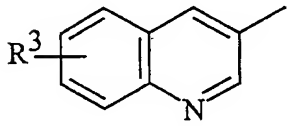

wherein R^3 is as defined above,

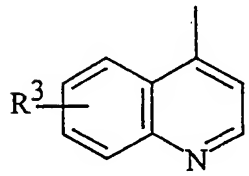

wherein R^3 is as defined above,

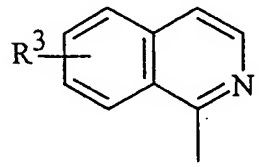

wherein R^3 is as defined above,

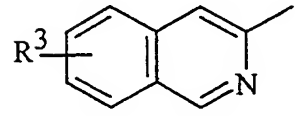

wherein R^3 is as defined above,

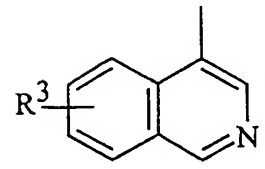

wherein R^3 is as defined above,

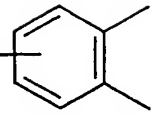

wherein R^3 is as defined above,

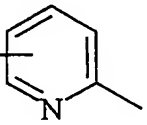

wherein R^3 is as defined above,


wherein R^3 is as defined above,


wherein R^3 is as defined above, or


wherein R^3 is as defined above, with the proviso that

when A is  wherein R^3 is hydrogen, methyl, or chloro,

R^1 is not  wherein R^3 is hydrogen; and

R^2 is CF_3,

CCl_3,

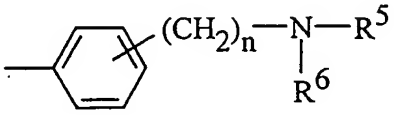
CBr_3, or

$-N(R^{11})-R^{10}$ wherein R^{10} is

hydrogen,

alkyl,

aralkyl, or



wherein n, R^5, and R^6 are as defined above, and

R^{11} is $-(CH_2)_m-N(R^6)-R^5$ wherein R^5, R^6, and m are as defined above,

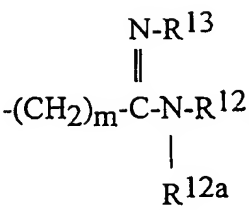
$-(CH_2)_m-N-C(=N-R^{13})-N-R^{12}$ wherein R^{12} and R^{12a} are each independently the same or different and are hydrogen,

alkyl,

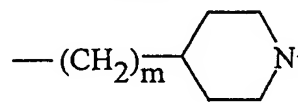
or aryl, and

R^{13} is hydrogen or alkyl, and

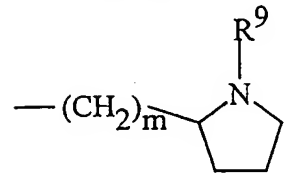
m is as defined above,



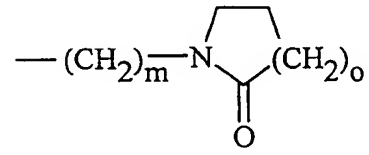
wherein m, R^{12}, R^{12a}, and R^{13} are as defined above,



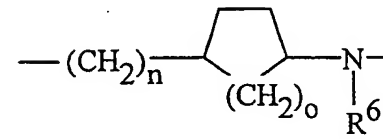
wherein R^9 and m are as defined above,



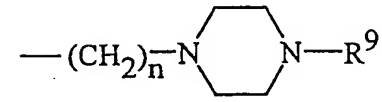
wherein R^9 and m are as defined above,



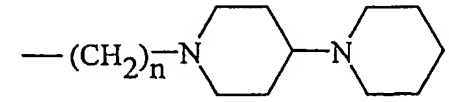
wherein m and o are as defined above,



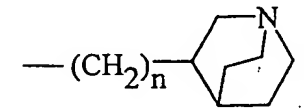
wherein n, o, R^5, and R^6 are as defined above,



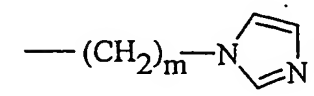
wherein n and R^9 are as defined above,



wherein n is as defined above,



wherein n is as defined above,

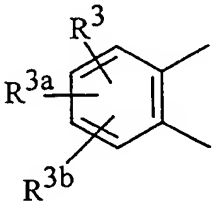


wherein m is as defined above, or

R^{10} and R^{11} when taken together can form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 is as defined above;

or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein A is selected from the group consisting of:



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

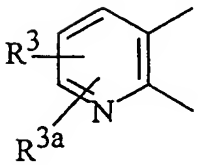
halogen,

CF_3,

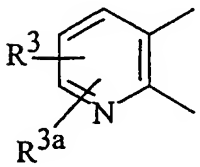
CBr_3,

CCl_3, or

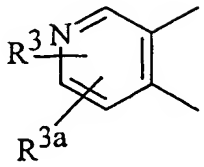
NO_2,

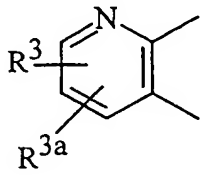


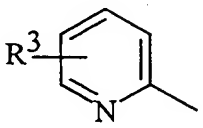
wherein R^3 and R^{3a} are as defined above,

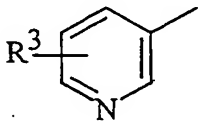


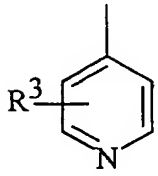
wherein R^3 and R^{3a} are as defined above,

 wherein R^3 and R^{3a} are as defined above, or

 wherein R^3 and R^{3a} are as defined above;

R^1 is  wherein R^3 is as defined above,

 wherein R^3 is as defined above,

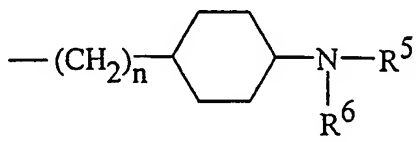
 wherein R^3 is as defined above; and

R^2 is CF_3,

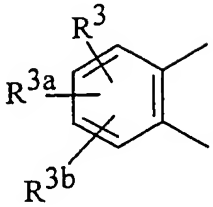
CCl_3,

CBr_3, or

$-N(R^{10})-R^{11}$ wherein R^{10} is hydrogen and

R^{11} is $-(CH_2)_n-N(R^6)-R^5$ wherein n, R^5, and R^6 are as defined above, or  wherein n, R^5, and R^6 are as defined above.

3. The compound of Claim 2 wherein A is



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein

R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

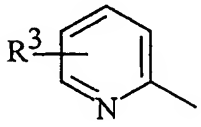
halogen,

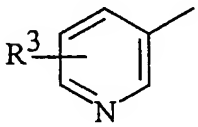
CF_3,

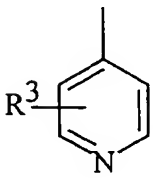
CBr_3,

CCl_3, or

NO_2;

R^1 is  wherein R^3 is as defined above,

 wherein R^3 is as defined above, or

 wherein R^3 is as defined above; and

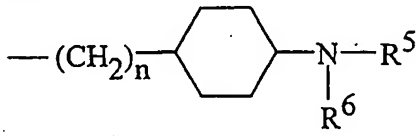
R^2 is CF_3,

CCl_3,

CBr_3, or

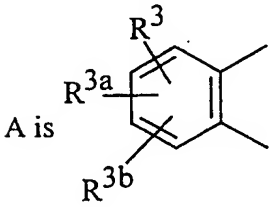
$-N(R^{11})-R^{10}$ wherein R^{10} is hydrogen and

R^{11} is $-(CH_2)_n-N(R^6)-R^5$ wherein n, R^5, and R^6 are as defined above, or



wherein n, R^5, and R^6 are as defined above.

4. The compound of Claim 3 wherein

A is  wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein

R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8

are each independently the same or different and are

hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

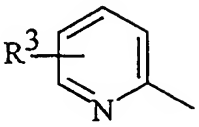
halogen,

CF_3,

CBr_3,

CCl_3, or

NO_2;

R^1 is  wherein R^3 is as defined above; and

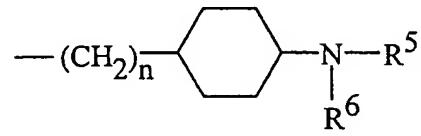
R^2 is CF_3,

CCl_3,

CBr_3, or

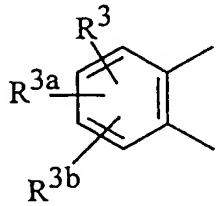
$-N-R^{10}$ wherein R^{10} is hydrogen and
|
R^{11}

R^{11} is $-(CH_2)_n-N-R^5$ wherein n, R^5, and R^6 are as defined
|
R^6

above, or  wherein n, R^5,

and R^6 are as defined above.

5. The compound of Claim 4 wherein

A is  wherein R^3, R^{3a}, and R^{3b} are each independently

the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined

above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

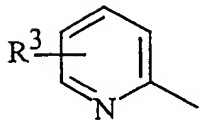
halogen,

CF_3,

CBr_3,

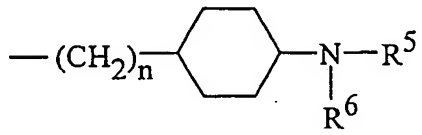
CCl_3, or

NO_2;

R^1 is  wherein R^3 is as defined above; and

R^2 is $-N(R^{10})(R^{11})$ wherein R^{10} is hydrogen and

R^{11} is $-(CH_2)_n-N(R^6)-R^5$ wherein n, R^5, and R^6 are as defined above,

or  wherein n, R^5, and R^6 are as defined above.

6. A compound which is selected from the group consisting of:

N-(1-azabicyclo[2.2.2]octan-3-yl)-3-(2-pyridinyl)-2-quinoxalinamine;

N-[3-(1H-imidazol-1-yl)propyl]-3-(2-pyridinyl)-2-quinoxalinamine;

N-[2-(1-methyl-2-pyrrolidinyl)ethyl]-3-(2-pyridinyl)-2-quinoxalinamine;

1-[3-[[3-pyridinyl)-2-quinoxalinamine]amino]propyl]-2-pyrrolidinone;

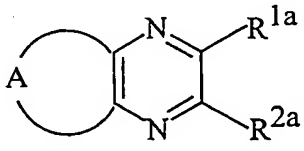
N-[4-(4-morpholinyl)phenyl]-3-(2-pyridinyl)-2-quinoxalinamine;

N-(4-piperidinylmethyl)-3-(2-pyridinyl)-2-quinoxalinamine;

N-[4-(dimethylamino)phenyl]-3-(2-pyridinyl)-2-quinoxalinamine; and

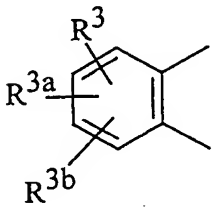
N-methyl-N-[4-[[3-(2-pyridinyl)-2-quinoxalinyl]amino]phenyl]-acetamide.

7. A method of treating a chemokine-mediated disease state, wherein the chemokine binds to an IL-8a (CXCR1) or b (CXCR2) receptor in a mammal, which comprises administering to said mammal an effective amount of a compound of Formula II



II

wherein A is selected from the group consisting of:



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N-R^5$ wherein R^5 and R^6 are each the same or different and are hydrogen,

R^6

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are

hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above

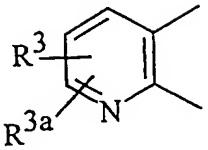
halogen,

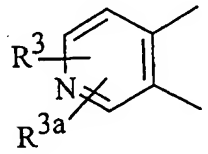
CF_3,

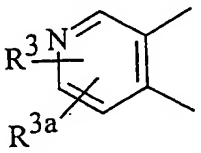
CBr_3,

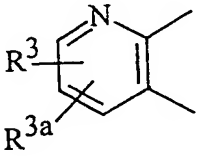
CCl_3, or

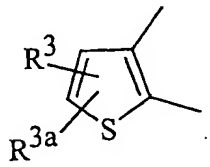
NO_2,

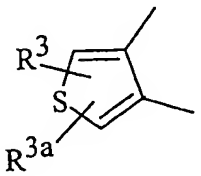

wherein R^3 and R^{3a} are as defined above,

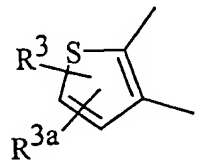

wherein R^3 and R^{3a} are as defined above,

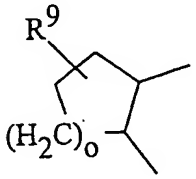

wherein R^3 and R^{3a} are as defined above,

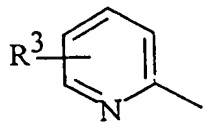

wherein R^3 and R^{3a} are as defined above,

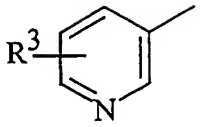

wherein R^3 and R^{3a} are as defined above,

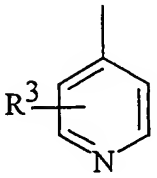

wherein R^3 and R^{3a} are as defined above,

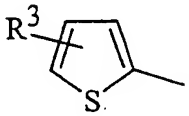

wherein R^3 and R^{3a} are as defined above,

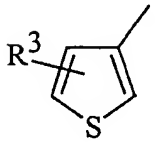

wherein o is an integer of 1 or 2, and R^9 is hydrogen or alkyl;

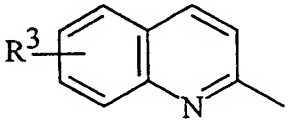
R^{1a} is 
wherein R^3 is as defined above,

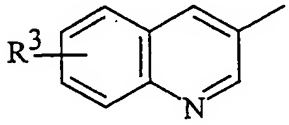

wherein R^3 is as defined above,

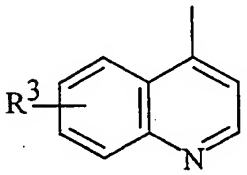

wherein R^3 is as defined above,

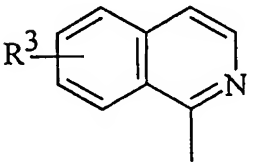

wherein R^3 is as defined above,

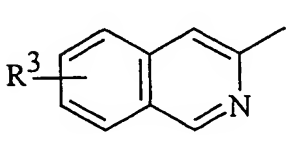

wherein R^3 is as defined above,

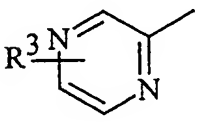

wherein R^3 is as defined above,

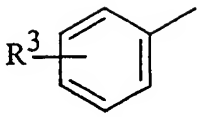

wherein R^3 is as defined above,


wherein R^3 is as defined above,


wherein R^3 is as defined above,


wherein R^3 is as defined above,


wherein R^3 is as defined above,

 wherein R^3 is as defined above,

alkyl,

OR^4 wherein R^4 is as defined above, or

$-(CH_2)_n-N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above; and

R^{2a} is CF_3,

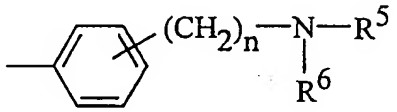
CCl_3,

CBr_3, or

$-N(R^{11})-R^{10}$ wherein R^{10} is hydrogen,

alkyl,

aralkyl, or



wherein n, R^5, and R^6 are as defined above,

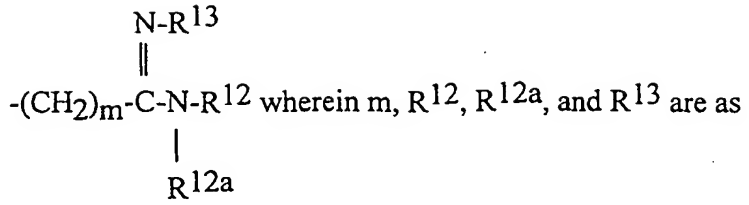
and

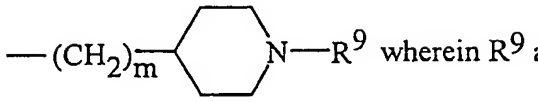
R^{11} is $-(CH_2)_m-N(R^6)-R^5$ wherein R^5, R^6, and m are as defined above,

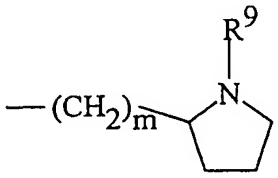
$-(CH_2)_m-N-C(=N-R^{13})-N-R^{12}$ wherein R^{12} and R^{12a} are each independently the same or different and are hydrogen, alkyl, or aryl, and

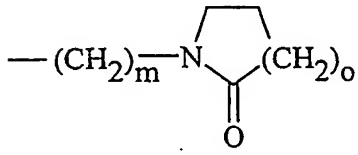
R^{13} is hydrogen or alkyl, and

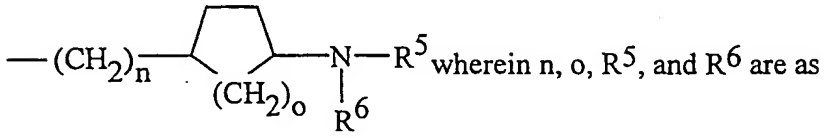
m is as defined above,

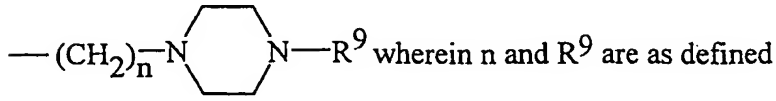

defined above,

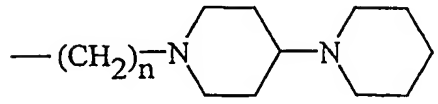

wherein R^9 and m are as defined above,

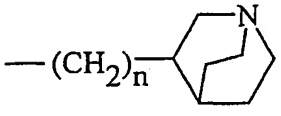

wherein R^9 and m are as defined above,

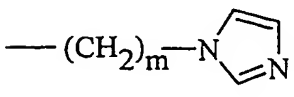

wherein m and o are as defined above,


wherein n, o, R^5, and R^6 are as defined above,


wherein n and R^9 are as defined above,


wherein n is as defined above,

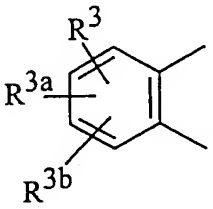

wherein n is as defined above,


wherein m is as defined above, or

R^{10} and R^{11} when taken together can form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 is as defined above;

or a pharmaceutically acceptable salt thereof.

8. The compound of Claim 7 wherein A is selected from the group consisting of:



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

-OR^4 wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein

R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8

are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

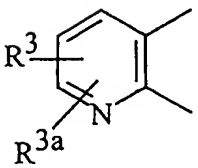
halogen,

CF_3,

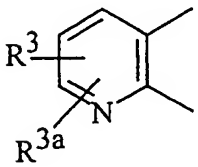
CBr_3,

CCl_3, or

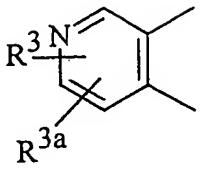
NO_2,

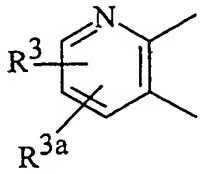


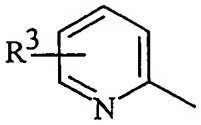
wherein R^3 and R^{3a} are as defined above,

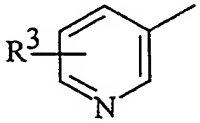


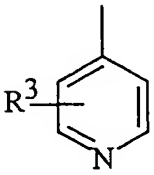
wherein R^3 and R^{3a} are as defined above,


wherein R^3 and R^{3a} are as defined above, or


wherein R^3 and R^{3a} are as defined above;

R^{1a} is 
wherein R^3 is as defined above,


wherein R^3 is as defined above, or


wherein R^3 is as defined above; and

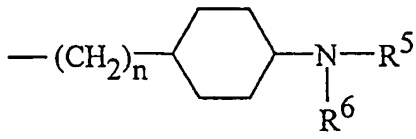
R^{2a} is CF_3,

CCl_3,

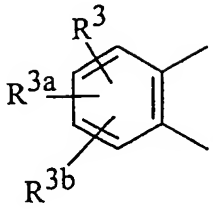
CBr_3, or

-N-R^{10} wherein R^{10} is hydrogen and
|
R^{11}

R^{11} is -$(CH_2)_n$-N-R^5 wherein n, R^5, and R^6 are as defined
|
R^6

above, or 
wherein n, R^5, and R^6 are as defined above.

9. The compound of Claim 8 wherein A is



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined

above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

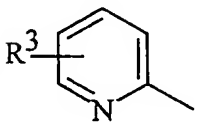
halogen,

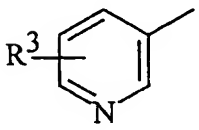
CF_3,

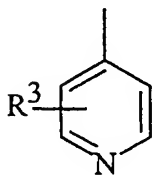
CBr_3,

CCl_3, or

NO_2;

R^{1a} is  wherein R^3 is as defined above,

 wherein R^3 is as defined above, or

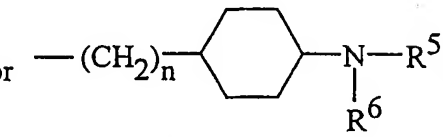
 wherein R^3 is as defined above; and

R^{2a} is CF_3,

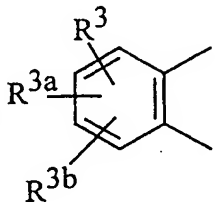
CCl_3,

CBr_3, or

$-N(R^{11})-R^{10}$ wherein R^{10} is hydrogen and

R^{11} is $-(CH_2)_n-N(R^6)-R^5$ wherein n, R^5, and R^6 are as defined above, or  wherein n, R^5, and R^6 are as defined above.

10. The compound of Claim 9 wherein

A is  wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

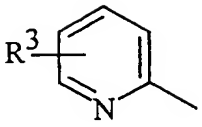
$-(CH_2)_m-N(R^6)-R^5$ wherein

R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8
$\quad\quad\quad

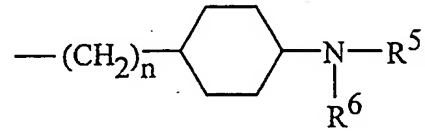
R^{1a} is  wherein R^3 is as defined above; and

R^{2a} is CF_3,

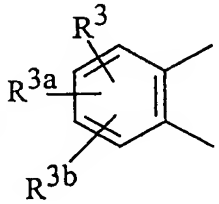
CCl_3,

CBr_3, or

$-N(R^{10})-R^{11}$ wherein R^{10} is hydrogen and

R^{11} is $-(CH_2)_n-N(R^6)-R^5$ wherein n, R^5, and R^6 are as defined above, or  wherein n, R^5, and R^6 are as defined above.

11. The compound of Claim 10 wherein

A is  wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are each the same

or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8

are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

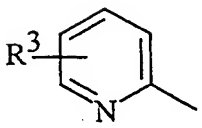
halogen,

CF_3,

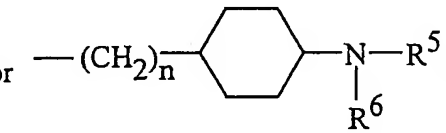
CBr_3,

CCl_3, or

NO_2;

R^{1a} is  wherein R^3 is as defined above; and

R^{2a} is $-N(R^{11})-R^{10}$ wherein R^{10} is hydrogen and

R^{11} is $-(CH_2)_n-N(R^6)-R^5$ wherein n, R^5, and R^6 are as defined above, or  wherein n, R^5, and R^6 are as defined above.

12. The method according to Claim 7 wherein the mammal is affected with a chemokine-mediated disease selected from the group consisting of psoriasis, or atopic dermatitis, disease associated with pathological angiogenesis (i.e. cancer), asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulo-nephritis, or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections.

13. The method according to Claim 7 wherein the compound or a pharmaceutically acceptable salt thereof is selected from group consisting of:

N′-[6-Chloro-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-diethyl-1,2-ethanediamine;

N′-[7-Chloro-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-diethyl-1,2-ethanediamine;

N′-[6,7-Dichloro-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-diethyl-1,2-ethanediamine;

6,7-Dichloro-3-(2-pyridinyl)-N-[3-(1-pyrrolidinyl)propyl]-2-quinoxalinamine;

6-Chloro-3-(2-pyridinyl)-N-[2-(1-pyrrolidinyl)ethyl]-2-quinoxalinamine;

7-Chloro-3-(2-pyridinyl)-N-[2-(1-pyrrolidinyl)ethyl]-2-quinoxalinamine;

N′-[6,7-Dimethyl-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-diethyl-1,2-ethanediamine;

6-Chloro-3-(2-pyridinyl)-N-[3-(1-pyrrolidinyl)propyl]-2-quinoxalinamine;

7-Chloro-3-(2-pyridinyl)-N-[3-(1-pyrrolidinyl)propyl]-2-quinoxalinamine;

N′-[6,7-Dimethyl-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-dimethyl-1,3-propanediamine;

N′-[6-Chloro-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-dimethyl-1,3-propanediamine;

N′-[7-Chloro-3-(2-pyridinyl)-2-quinoxalinyl]-N,N-dimethyl-1,3-propanediamine;

6-Chloro-N-[4-(dimethylamino)cyclohexyl]-3-(2-pyridinyl)-2-quinoxalinamine;

7-Chloro-N-[4-(dimethylamino)cyclohexyl]-3-(2-pyridinyl)-2-quinoxalinamine;

2,6,7-Trimethyl-3-piperazin-1-yl-quinoxaline;

N,N-Dimethyl-N′-(3-methyl-quinoxalin-2-yl)-propane-1,3-diamine;

2-Methyl-3-(4-methyl-piperazin-1-yl)-quinoxaline;

2-Ethyl-3-piperazin-1-yl-quinoxaline;

6,7-Dichloro-2-methyl-3-piperazin-1-yl-quinoxaline;

2-Phenyl-3-piperidin-1-yl-quinoxaline;

Benzyl-(3-phenyl-quinoxalin-2-yl)-amine;

Phenyl-(3-phenyl-quinoxalin-2-yl)-amine;

Methyl-(3-phenyl-quinoxalin-2-yl)-amine;

3-Phenyl-quinoxalin-2-ylamine;

2-Methyl-3-piperazin-1-yl-quinoxaline;

2-Methyl-3-piperidino-quinoxaline;

5-[4-(3-Methyl-quinoxalin-2-yl)-piperazin-1-yl]-pentan-1-ol;

N,N-Dimethyl-N′-(3-methyl-quinoxalin-2-yl)-ethane-1,2-diamine;

N,N-Diethyl-N′-(3-methyl-quinoxalin-2-yl)-ethane-1,2-diamine;

(3-Methyl-quinoxalin-2-yl)-(3-morpholin-4-yl-propyl)-amine;

N,N-Dimethyl-N′-(3-phenyl-quinoxalin-2-yl)-propane-1,3-diamine;

3-Phenyl-quinoxalin-2-ylamine;

2-Methyl-3-pyrrolidin-1-yl-quinoxaline;

N-(1-Azabicyclo[2.2.2]octan-3-yl)-3-(2-pyridinyl)-2-quinoxalinamine;

N-[3-(1H-Imidazol-1-yl)propyl]-3-(2-pyridinyl)-2-quinoxalinamine;

N-[2-(1-Methyl-2-pyrrolidinyl)ethyl]-3-(2-pyridinyl)-2-quinoxalinamine;

1-[3-[[3-Pyridinyl)-2-quinoxalinamine]amino]propyl]-2-pyrrolidinone;

N-[4-(4-Morpholinyl)phenyl]-3-(2-pyridinyl)-2-quinoxalinamine;

N-(4-Piperidinylmethyl)-3-(2-pyridinyl)-2-quinoxalinamine;

N-[4-(Dimethylamino)phenyl]-3-(2-pyridinyl)-2-quinoxalinamine;

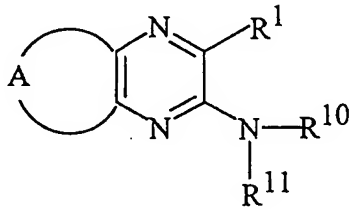
and

N-Methyl-N-[4-[[3-(2-pyridinyl)-2-quinoxalinyl]amino]phenyl]-acetamide.

14. A pharmaceutical composition comprising a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

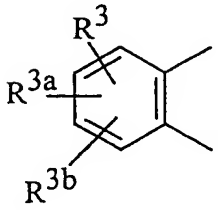
15. A pharmaceutical composition adapted for administration as an agent for treating psoriasis, or atopic dermatitis, disease associated with pathological angiogenesis (i.e. cancer), asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, gastric ulcer, septic shock, endotoxic shock, gram-negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulo-nephritis, or thrombosis, Alzheimer's disease, graft versus host reaction, or allograft rejections comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

16. A method for preparing a compound having the Formula Ia



Ia

wherein A is selected from the group consisting of:



wherein R^3, R^{3a}, and R^{3b} are each independently the same or different and are hydrogen,

alkyl,

$-OR^4$ wherein R^4 is hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein

R^5 and R^6 are each the same or different and are hydrogen,

alkyl, acetyl, or

R^5 and R^6 are taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 is as defined above and m is an integer of 2 to 5,

$-(CH_2)_n-N(R^8)-R^7$ wherein n is zero or an integer of 1 and R^7 and R^8 are each independently the same or different and are hydrogen,

alkyl,

aryl,

aralkyl,

acetyl, or

$-(CH_2)_m-N(R^6)-R^5$ wherein R^5 and R^6 are as defined above or R^7 and R^8 taken together to form a 5- to 7-membered ring optionally containing an oxygen atom or $N-R^4$ wherein R^4 and m are as defined above,

$-(CH_2)_n-CON(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2N(R^8)-R^7$ wherein R^7, R^8, and n are as defined above,

$-(CH_2)_n-SO_2OR^4$ wherein R^4 and n are as defined above,

$-(CH_2)_n-CO_2R^4$ wherein R^4 and n are as defined above,

$-CH_2OR^4$ wherein R^4 is as defined above,

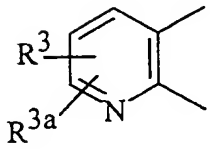
halogen,

CF_3,

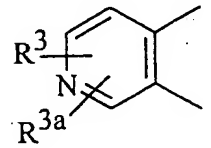
CBr_3,

CCl_3, or

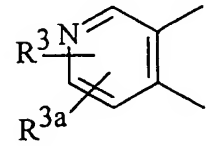
NO_2,



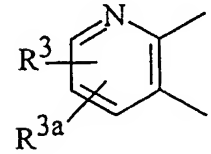
wherein R^3 and R^{3a} are as defined above,



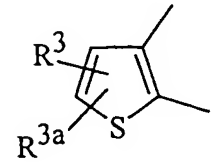
wherein R^3 and R^{3a} are as defined above,



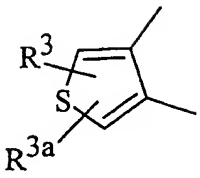
wherein R^3 and R^{3a} are as defined above,

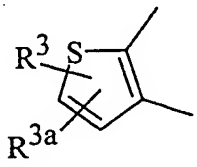


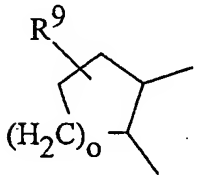
wherein R^3 and R^{3a} are as defined above,

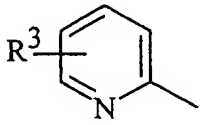


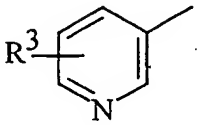
wherein R^3 and R^{3a} are as defined above,

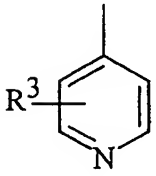
 wherein R^3 and R^{3a} are as defined above,

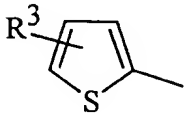
 wherein R^3 and R^{3a} are as defined above,

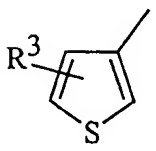
 wherein o is an integer of 1 or 2, and R^9 is hydrogen or alkyl;

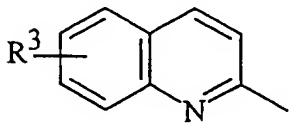
R^1 is  wherein R^3 is as defined above,

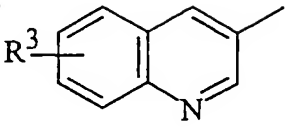
 wherein R^3 is as defined above,

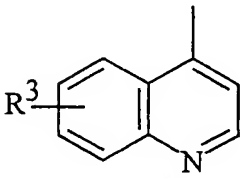
 wherein R^3 is as defined above,

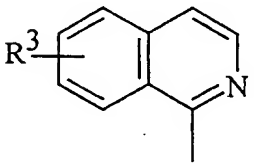
 wherein R^3 is as defined above,

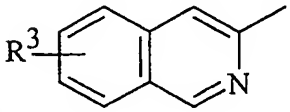
 wherein R^3 is as defined above,

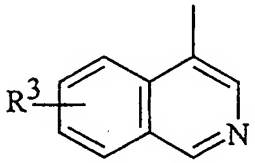
 wherein R^3 is as defined above,

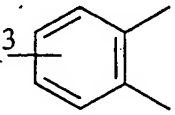
 wherein R^3 is as defined above,

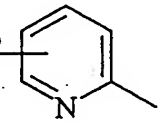
 wherein R^3 is as defined above,

 wherein R^3 is as defined above,

 wherein R^3 is as defined above, or

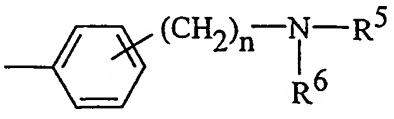
 wherein R^3 is as defined above, with the proviso that

when A is  wherein R^3 is hydrogen, methyl, or chloro;

R^1 is not  wherein R^3 is hydrogen;

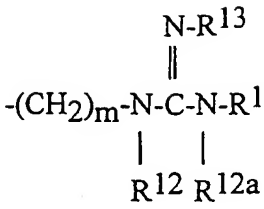
R^{10} is hydrogen,

alkyl,

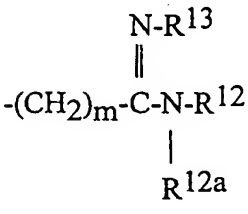
aralkyl, or 

wherein n, R^5, and R^6 are as defined above; and

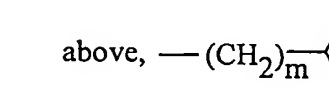
R^{11} is $-(CH_2)_m-N(R^6)-R^5$ wherein R^5, R^6, and m are as defined above,



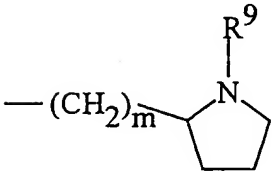
wherein R^{12} and R^{12a} are each independently the same or different and are hydrogen, alkyl, or aryl, and R^{13} is hydrogen or alkyl, and m is as defined above,



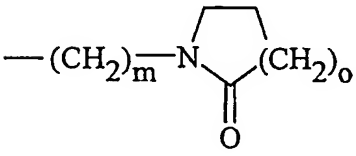
wherein m, R^{12}, R^{12a}, and R^{13} are as defined above,



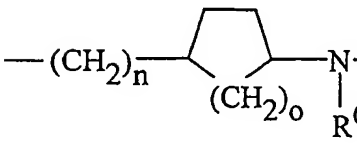
wherein R^9 and m are as defined above,



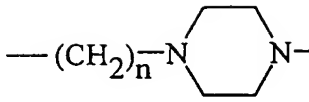
wherein R^9 and m are as defined above,

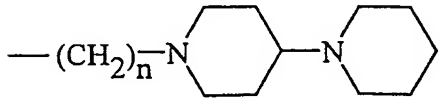


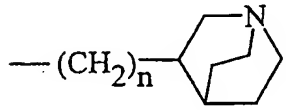
wherein m and o are as defined above,

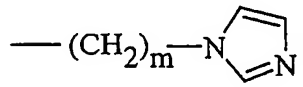


wherein n, o, R^5, and R^6 are as defined above,

 wherein n and R^9 are as defined above,

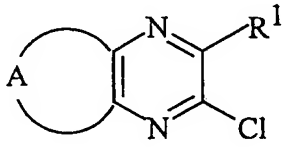
 wherein n is as defined above,

 wherein n is as defined above,

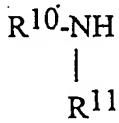
 wherein m is as defined above, or

R^{10} and R^{11} when taken together can form a 5- to 7-membered ring optionally containing an oxygen atom or N-R^4 wherein R^4 is as defined above;

or a pharmaceutically acceptable salt thereof comprises reacting a compound of Formula III

 III

wherein A and R^1 are as defined above with a compound of Formula IV

 IV

wherein R^{10} and R^{11} are as defined above in a solvent to afford a compound of Formula Ia.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/26707

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 C07D401/14 C07D453/02 C07D241/44 C07D471/04
C07D495/04 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ED. ELSLAGER ET AL.: "POTENTIAL ANTIMALARIAL AGENTS." JOURNAL OF MEDICINAL CHEMISTRY., vol. 11, no. 3, May 1968, pages 630-631, XP002100497 WASHINGTON US see page 630 - page 631 ---	1-5, 14-16
X	M.LORIGA ET AL.: "QUINOXALINE CHEMISTRY.PART 5." FARMACO., vol. 51, no. 8,9, 1996, pages 559-568, XP002100498 PAVIA IT see page 559 - page 561 ---	1,7, 13-16

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 1999	06/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/26707

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication.where appropriate, of the relevant passages	Relevant to claim No.
X	S.PIRAS,M.LORIGA: "QUINOXALINE CHEMISTRY,PART 6-" FARMACO., vol. 51, no. 8,9, May 1968, pages 569-577, XP002100499 PAVIA IT see page 569 - page 571 ---	1,7-16
X	J. METZNER ET AL.: "ANTIMIKROBIELLE WIRKSAMKEIT AUSGEWÄHLTER CHINOXALINE" PHARMAZIE., vol. 36, no. H5, 1981, pages 368-370, XP002100500 BERLIN DD see page 368 - page 369 ---	13-15
X	CHEMICAL ABSTRACTS, vol. 123, no. 28, 1995 Columbus, Ohio, US; abstract no. 55808h, A.MONGE ET AL.: "NEW 5-HT3 ANTAGONISTS." page 917; column 1; XP002100501 see abstract & AN.R.ACAD.FARM., vol. 60, no. 1, 1994, pages 91-104, ---	13-15
A	CHEMICAL ABSTRACTS, vol. 89, no. 28, 1978 Columbus, Ohio, US; abstract no. 163550f, G.K. MITRA ET AL.: "SEARCH FOR POSSIBLE ANTIPROTOZOAL COMPOUNDS IN THE QUINOXALINE SERIE." page 575; XP002100502 see abstract & J. INDIAN CHEM. SOC., vol. 55, no. 4, 1978, pages 422-424, INDIA ---	1,6-16
X	DE 22 05 815 A (HOECHST) 16 August 1973 see page 5; claims 1,3; example 1.31 ---	13-15
A	FR 2 081 540 A (CIBA-GEIGY) 3 December 1971 see claims; example 13 ---	1,7, 13-16
A	FR 2 206 951 A (PFIZER) 14 June 1974 see the whole document -----	1,7-15

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INTERNATIONAL SEARCH REPORT

[redacted]tional application No.
PCT/US 98/26707

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7-13
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 7-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

onal Application No
PCT/US 98/26707

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2205815 A	16-08-1973	NONE	
FR 2081540 A	03-12-1971	AT 308116 B	15-05-1973
		AT 307424 B	15-04-1973
		BE 763377 A	24-08-1971
		DE 2107301 A	09-09-1971
		NL 7102469 A	27-08-1971
		OA 3687 A	24-12-1971
		ZA 7101072 A	27-10-1971
FR 2206951 A	14-06-1974	BE 807526 A	20-05-1974
		DE 2357186 A	22-05-1974
		GB 1457400 A	01-12-1976
		GB 1457005 A	01-12-1976
		JP 1012584 C	29-08-1980
		JP 49133384 A	21-12-1974
		JP 55004100 B	29-01-1980
		NL 7315808 A	22-05-1974

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